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# GLYCAEMIC EFFECTS OF TRADITIONAL EUROPEAN PLANT TREATMENTS FOR DIABETES. STUDIES IN NORMAL AND STREPTOZOTOCIN DIABETIC MICE

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SUMMARY Twelve plants used for the traditional treatment of diabetes mellitus in northern Europe were studied using normal and streptozotocin diabetic mice to evaluate effects on glucose homeostasis. The plants were administered in the diet (6·25% by weight) and/or as decoctions or infusions in place of drinking water, to coincide with the traditional method of preparation. Treatment for 28 days with preparations of burdock (Arctium lappa), cashew (Anacardium occidentale), dandelion (Taraxacum officinale), elder (Sambucus nigra), fenugreek (Trigonella foenum-graecum), guayusa (Ilex guayusa), hop (Humulus lupulus), nettle (Urtica dioica), cultivated mushroom (Agaricus bisporus), periwinkle (Catharanthus roseus), sage (Salvia officinale), and wild carrot (Daucus carrota) did not affect the parameters of glucose homeostasis examined in normal mice (basal plasma glucose and insulin, glucose tolerance, insulin-induced hypoglycaemia and glycated haemoglobin). After administration of streptozotocin (200 mg/kg) burdock and nettle aggravated the diabetic condition, while cashew, dandelion, elder, fenugreek, hop, periwinkle, sage and wild carrot did not significantly affect the parameters of glucose homeostasis studied (basal glucose and insulin, insulin-induced hypoglycaemia, glycated haemoglobin and pancreatic insulin concentration). Guayusa and mushroom retarded the development of hyperglycaemia in streptozotocin diabetes and reduced the hyperphagia, polydipsia, body weight loss, and glycated haemoglobin. Mushroom also countered the initial reduction in plasma insulin and the reduction in pancreatic insulin concentration, and improved the hypoglycaemic effect of exogenous insulin. These studies suggest the presence of potentially useful antidiabetic agents in guayusa and mushroom.

*Key words:* Antidiabetic plants, hypoglycaemic, diabetic mice

## INTRODUCTION

THE USE of traditional plant treatments for diabetes mellitus has largely disappeared in Europe since the introduction of insulin, although some medical herbalists and natural treatment enthusiasts use them, mostly as adjuncts to conventional therapy (1, 2). Few of the traditional plant treatments for diabetes have received scientific or medical scrutiny, and the World Health Organization has recommended that this should be undertaken (3, 4). This paper describes a study of 12 traditional antidiabetic plant treatments used in northern Europe. A possible hypoglycaemic effect was investigated in normal and streptozotocin diabetic mice.

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## MATERIALS AND METHODS

### *Animals*

Adult male lean mice from a colony bred at Aston University (5) were housed in an air-conditioned room at 22±2°C and supplied with a standard pellet diet (Spratts Laboratory Diet 1, Lillico Ltd., Reigate UK) and water *ad lib.*

### *Traditional Antidiabetic Plants*

Dried leaves of burdock (Arctium lappa), elder (Sambucus nigra), hop (Humulus lupulus), nettle (Urtica dioica), periwinkle (Catharanthus roseus), sage (Salvia officinale) and wild carrot (Daucus carrota); dried roots and leaves of dandelion (Taraxacum officinale); seeds of fenugreek

(Trigonella foenum-graecum) and cashew nuts (Anacardium occidentale) were obtained from retail health food stores in Birmingham. Dried fruiting bodies of cultivated mushroom (Agaricus bisporus) were obtained from a commercial source in Surrey. A concentrated aqueous herbal preparation from the leaves of Ilex guayusa, termed guayusa, was obtained from the British Diabetic Association, London, who received it from a French Druid Herbalist.

All plants except guayusa were supplied as 6·25% by weight of the diet, prepared by mixing homogenized plant material with powdered standard diet and repelleting. In addition, burdock, dandelion, nettle, sage and hop were supplied as decoctions. These were prepared by addition of 1 g of plant material to 400 ml of cold water which was boiled for 5 min and infused for 15 min. Wild carrot, elder and periwinkle were supplied as infusions prepared by addition of 1 g of plant material to 400 ml of boiling water, and infused for 15 min. Decoctions and infusions were given in place of drinking water. Guayusa was diluted 1 ml in 100 ml of water and supplied in place of drinking water. In preliminary experiments control diets were supplemented with fibre (methyl cellulose) to correspond with the fibre content of the test diet. Since the small amounts of methyl cellulose involved (<6% by weight of the diet) did not affect the parameters studied compared with non-supplemented diet this practice was not continued.

*Experimental Design*

After a four-day run-in period, non-diabetic test mice were supplied with traditional plant treatment in the diet and/or as a replacement for drinking water as described above. Treatment was maintained throughout the experiment. After obtaining the blood sample on day 28, diabetes was induced using streptozotocin (Sigma Chemical Company, Poole, Dorset; 200 mg/kg ip in 0·5 mol/l citrate buffer, pH 4·5), and the experiment was continued until day 43. Body weight, food and fluid intake were monitored daily, and blood samples (50 µl) for plasma glucose and insulin determination were obtained from the tail tip of conscious non-fasted mice at intervals of 7-days. On day 21, a glucose tolerance test (2 g/kg glucose in a 40% w/v solution, ip, at time zero) was conducted. Blood samples were taken for plasma glucose and insulin assay at 0, 30 and 60 min. This was immediately followed by an insulin hypoglycaemia test (0·5 U/kg monocomponent porcine insulin (Actrapid, Novo Industria, Copenhagen), ip, at 60 min). A further blood sample (30 µl) was taken for plasma glucose assay at 100 min. A second insulin hypoglycaemia test was performed on day 42. During this test blood samples were taken immediately before and at 40 and 80 min after administration of 1 U/kg insulin ip. Blood (20 µl) for glycated haemoglobin analysis was taken on days 28 and 42 (before the insulin hypoglycaemia tests). Total pancreatic insulin content was determined on day 43.

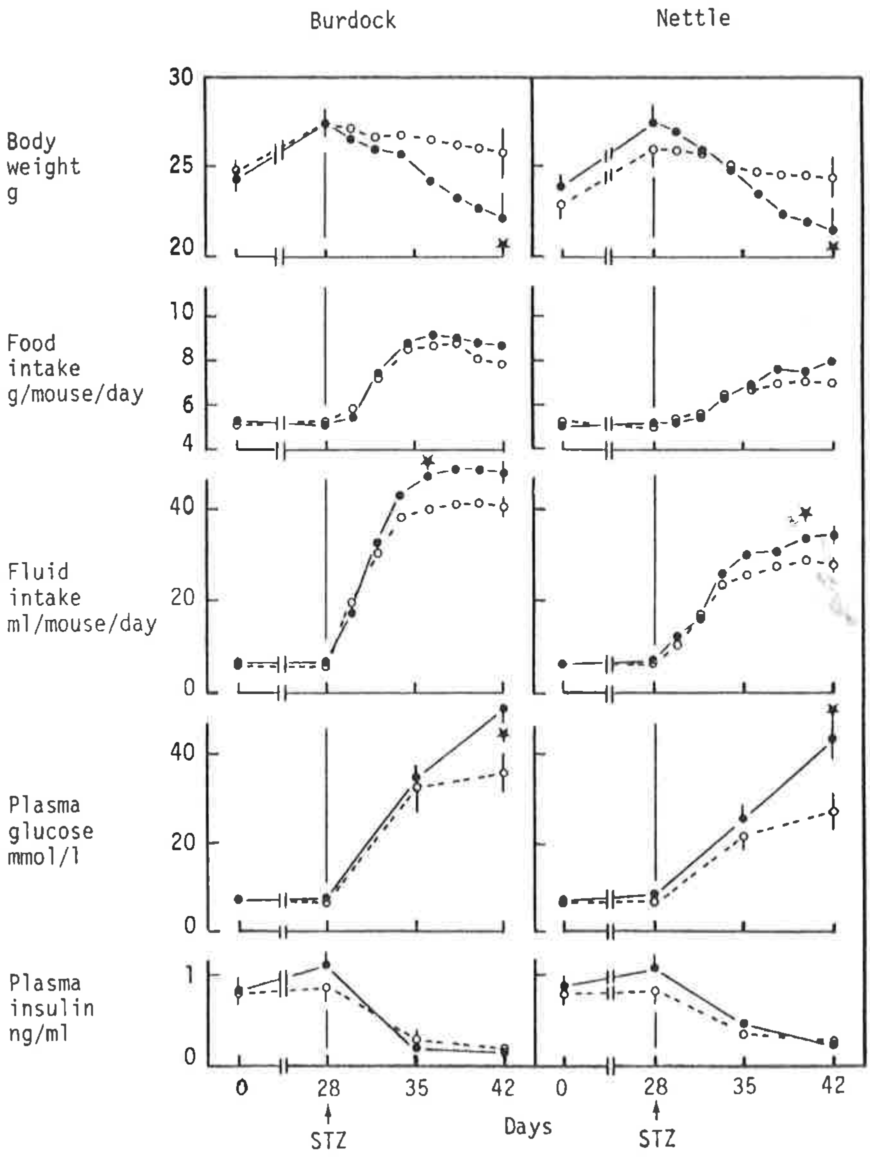


Figure 1. Effect of burdock and nettle (6·25% by weight of diet and 1 g/400 ml decoction as drinking fluid) on body weight, food and fluid intake, and plasma glucose and insulin concentrations in non-diabetic (days 0–28) and streptozotocin diabetic (days 28–42) mice. Control (○– –○); Test (●——●).

Values are mean ± SEM, n = 5. * $p < 0·05$ compared with control at this time and all subsequent times during the study.

*Analyses*

Plasma glucose was assayed using a glucose oxidase method and insulin was determined in plasma and acid-ethanol pancreatic extracts by radioimmunoassay (6). Glycated haemoglobin was measured by affinity chromatography using Glycogel B (7). Groups of data are expressed as mean ± SEM and compared using Student's t-test. Differences were considered to be significant if $p < 0{\cdot}05$.

## RESULTS

Administration of streptozotocin on day 28 increased basal plasma glucose concentrations, the percentage of glycated haemoglobin, food intake and fluid intake, accompanied by body weight loss and a reduction in basal plasma insulin concentrations (see values before and after streptozotocin in Figures 1 and 2).

*Cashew, Dandelion, Elder, Fenugreek, Hop, Periwinkle, Sage, Wild Carrot*

Treatment with each of these plants did not affect the parameters of glucose homeostasis measured in non-diabetic and streptozotocin diabetic mice (data not shown). There were no significant changes in basal plasma glucose and insulin concentrations, glucose tolerance, insulin-induced hypoglycaemia, and glycated haemoglobin in non-diabetic mice. Also there were no significant changes in basal plasma glucose and insulin concentrations, glycated haemoglobin, insulin-induced hypoglycaemia and pancreatic insulin concentrations in streptozotocin diabetic mice. Elder, hop and periwinkle increased ($p < 0{\cdot}05$) fluid intake in non-diabetic mice by about 25, 45 and 95% respectively (data not shown). Conversely hop decreased (about 30%, $p < 0{\cdot}05$) fluid intake in diabetic mice (data not shown). Fenugreek retarded the rate of body weight loss in diabetic mice (decrease in body weight of 11% by day 42 compared with a decrease of 31% in control group; $p < 0{\cdot}05$; data not shown). The pancreatic insulin concentration was not affected by these plant treatments (data not shown).

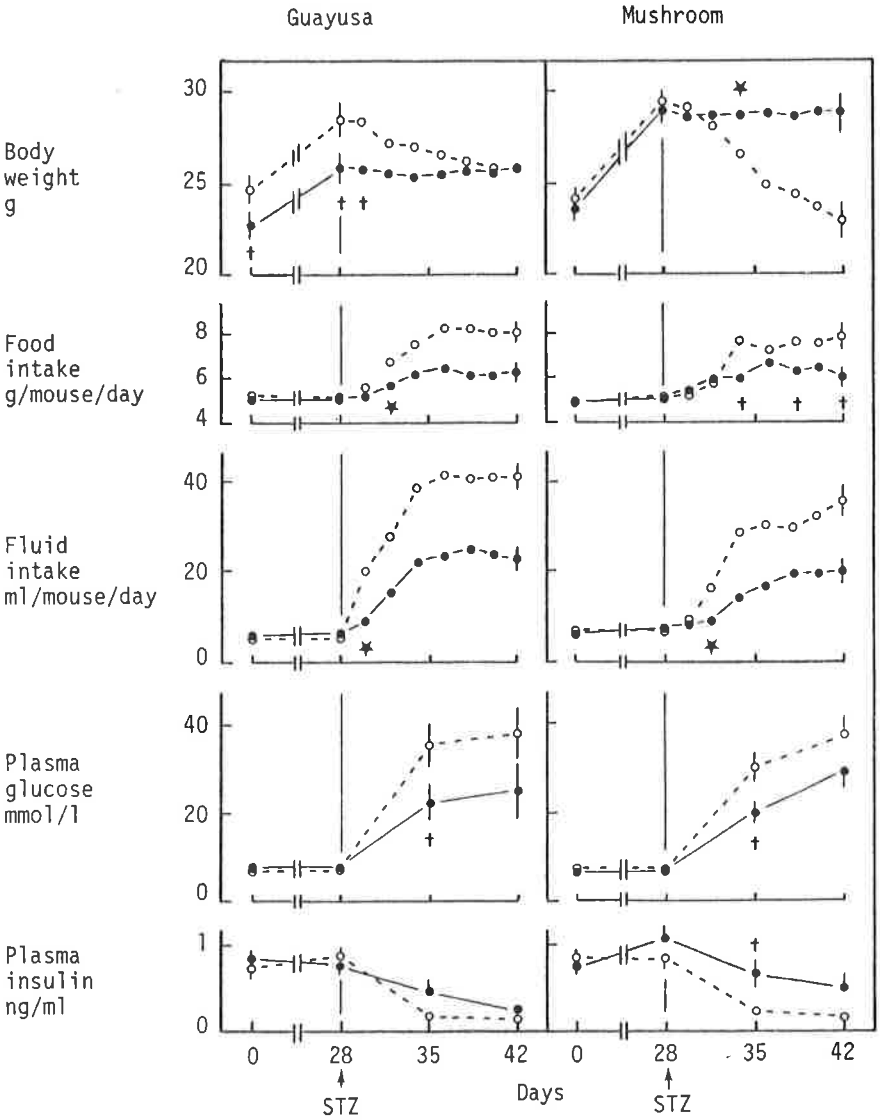


Figure 2. Effect of guayusa (1:100 dilution of herbal preparation as drinking fluid) and mushroom (6·25% by weight of diet) on body weight, food and fluid intake, and plasma glucose and insulin concentrations in non-diabetic (days 0–28) and streptozotocin diabetic (days 28–42) mice. Control (○- - -○); Test (●——●).

Values are mean ± SEM, n = 5. † $p < 0{\cdot}05$ compared with control at this time. * $p < 0{\cdot}05$ compared with control at this time and all subsequent times during the study.

*Burdock, Nettle*

These treatments did not affect the parameters of glucose homeostasis measured in non-diabetic mice, but they increased (41 and 68% respectively, $p < 0{\cdot}05$) basal glucose concentrations in streptozotocin diabetic mice by day 42 (Figure 1). Burdock and nettle also enhanced fluid intake and the rate of body weight loss in streptozotocin diabetes, indicating a more severely diabetic state (Figure 1). However, insulin-induced hypoglycaemia, the pancreatic insulin concentration and the percentage of glycated haemoglobin were not significantly altered (data not shown).

*Guayusa, Mushroom*

Guayusa and mushroom did not affect the parameters of glucose homeostasis measured in non-diabetic mice, but reduced the severity of hyperglycaemia during the first week after induction of streptozotocin diabetes (Figure 2). Although a significant antihyperglycaemic effect of these treatments was not evident in severely diabetic mice, the hyperphagia, polydipsia and body weight loss were reduced (Figure 2). The percentage glycated haemoglobin on day 42 was also reduced (guayusa $6{\cdot}2 \pm 1{\cdot}7\%$ vs control $9{\cdot}5 \pm 0{\cdot}3$, $n = 5$, $p < 0{\cdot}05$; mushroom $6{\cdot}8 \pm 0{\cdot}8\%$ vs control $9{\cdot}5 \pm 0{\cdot}5$, $n = 5$, $p < 0{\cdot}05$). Mushroom countered the initial reduction in plasma insulin concentrations after the induction of streptozotocin diabetes (Figure 2), and opposed the reduction in the pancreatic insulin concentrations on day 43 (pancreatic insulin concentration of $6{\cdot}5 \pm 0{\cdot}8$ µg/g wet weight vs control $3{\cdot}0 \pm 1{\cdot}0$ µg/g, $n = 5$, $p < 0{\cdot}05$). As shown in Figure 3 mushroom improved insulin-induced hypoglycaemia in streptozotocin diabetic mice. Guayusa did not significantly affect either the pancreatic insulin concentration or insulin-induced hypoglycaemia.

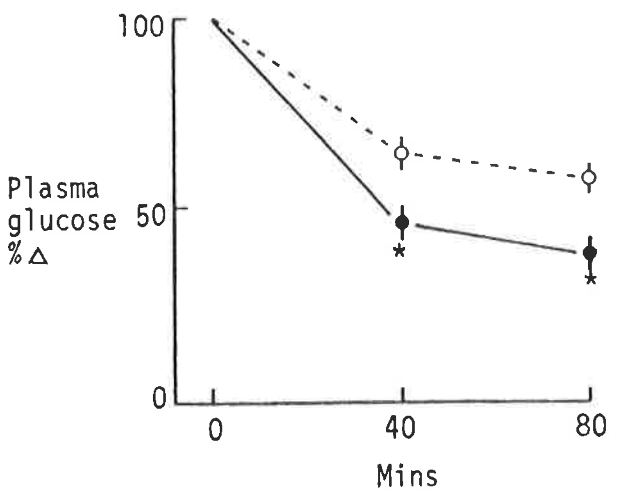


Figure 3. Effect of mushroom (6·25% by weight of diet) on insulin-induced hypoglycaemia (1 U/kg insulin ip at time zero) in streptozotocin diabetic mice on day 42. Data are presented as the percentage change in plasma glucose concentrations. Control (○- - ○); Test (●——●).

Values are mean ± SEM, n = 5, * $p < 0{\cdot}05$ compared with control.

## Discussion

Treatizes of folklore medicine (e.g., 8, 9, 10, 11, 12, 13) have described the use of cashew, dandelion, elder, fenugreek, hop, periwinkle, sage, wild carrot, burdock, nettle, and mushrooms as traditional treatments for diabetes in northern Europe. Most of the evidence for a beneficial effect of these plants is anecdotal. However fenugreek has been reported to lower glucose concentrations in normal and alloxan diabetic rats, rabbits and dogs (14–16) and a hypoglycaemic effect of periwinkle has been reported in normal animals (17). There have been claims and counter-claims for a beneficial antidiabetic effect of nettle tea (18, 19). Although guayusa, an extract of the leaves of Ilex guayusa, is used by Druids as a treatment for diabetes (Dalyon, personal communication to BDA, 1985) there are no scientific or medical reports of its efficacy.

Streptozotocin diabetes provides a condition of insulinopenia and insulin resistance which presents a demanding test for any potential hypoglycaemic agent (20, 21). In the present study, consumption of large amounts (6·25% by weight of the diet, plus decoctions or infusions (1 g/400 ml) as drinking fluid) of the leaves of elder, hop, periwinkle, sage and wild carrot, leaves and root of dandelion and fenugreek seeds did not affect the parameters of glucose homeostasis studied in normal and streptozotocin diabetic mice. However fenugreek, which reduced weight loss, hop which reduced polydipsia, and periwinkle all resulted in a healthy appearance of the diabetic mice as indicated by coat condition and physical activity. Thus, these treatments may offer some metabolic benefits other than improved glycaemic control. For example fenugreek exerts a hypocholesterolaemic effect in diabetic dogs (22). Although several weakly hypoglycaemic alkaloids have been isolated from periwinkle (17), treatment with this plant did not ameliorate the severe diabetes induced in the present study.

Burdock and nettle aggravated the hyperglycaemia, polydipsia and body weight loss in streptozotocin diabetic mice, indicating a detrimental effect on the diabetic condition. The antihyperglycaemic effect of guayusa and mushroom during the development of streptozotocin diabetes indicates an early beneficial effect of these plants. Consumption of guayusa and mushroom may offer a longer term advantage, as indicated by the lower glycated haemoglobin values at day 42. The action of mushroom may include a protective effect against islet B-cell destruction, since this treatment reduced the initial insulinopenic effect of streptozotocin and countered the depletion of pancreatic insulin at day 42. Mushroom also appears to exert a beneficial extrapancreatic effect by

enhancing the hypoglycaemic action of exogenous insulin.

The active principles in guayusa and mushroom are unestablished. However, guayusa contains guanidine, a known hypoglycaemic substance related to the biguanide class of oral antidiabetic drugs (23). Guanidine has been detected in the edible mushroom (24), and other species of mushroom (e.g., Amanita phalloides) have been reported to contain poisonous hypoglycaemic substances which deplete hepatic glycogen (25). Since there is no evidence of a harmful effect of the edible mushroom, it is possible that different non-toxic antihyperglycaemic substances may be responsible for the amelioration of diabetes by this mushroom. Extracts of the edible mushroom have been reported to affect islet B-cells by stimulating calcium uptake and insulin release (26). This has been attributed to a lectin (27, 28). Whether such a principle is responsible for the improvement of insulin-induced hypoglycaemia is undetermined, but the dual action of mushroom, like the sulphonylureas, to exert pancreatic and extrapancreatic effects may be particularly advantageous.

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